# The ageing systemic milieu negatively regulates neurogenesis and cognitive function.

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**Public Summary:**
The aging brain remains plastic and exercise or dietary changes can increase cognitive function in humans and animals, with animal brains showing a reversal of some of the aforementioned biological changes associated with aging. We show that a similar rejuvenation of the brain can be attained by pairing the circulatory system of an old with a young mouse through parabiosis or through repeated, intravenous infusion of blood plasma from young into old mice. The old brains showed increases in hippocampal neurogenesis while young mice exposed to old blood showed an accelerated aging phenotype,. We have identified several chemokines and immune factors linked to systemic inflammation sufficient to exert at least some of these effects. Our observations thus support the concept that systemic circulatory factors are sufficient to modulate brain function and processes related to brain aging. They also provide an opportunity and potential platform to identify "rejuvenating" factors and gain an understanding of the molecular basis of rejuvenation (and aging).

**Scientific Abstract:**
In the central nervous system, ageing results in a precipitous decline in adult neural stem/progenitor cells and neurogenesis, with concomitant impairments in cognitive functions. Interestingly, such impairments can be ameliorated through systemic perturbations such as exercise. Here, using heterochronic parabiosis we show that blood-borne factors present in the systemic milieu can inhibit or promote adult neurogenesis in an age-dependent fashion in mice. Accordingly, exposing a young mouse to an old systemic environment or to plasma from old mice decreased synaptic plasticity, and impaired contextual fear conditioning and spatial learning and memory. We identify chemokines--including CCL11 (also known as eotaxin)--the plasma levels of which correlate with reduced neurogenesis in heterochronic parabionts and aged mice, and the levels of which are increased in the plasma and cerebrospinal fluid of healthy ageing humans. Lastly, increasing peripheral CCL11 chemokine levels in vivo in young mice decreased adult neurogenesis and impaired learning and memory. Together our data indicate that the decline in neurogenesis and cognitive impairments observed during ageing can be in part attributed to changes in blood-borne factors.